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New Drugs in Cancer Chemotherapy

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New Natural Products Under Development at the National Cancer Institute

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Summary

Twenty-six new agents of natural products origin which are under preclinical development as potential antitumor agents at the National Cancer Institute are discussed with reference to their sources, structures, antitumor activity, current status, and future potential as clinically effective drugs.

Introduction

Since 1956 the Cancer Chemotherapy National Service Center, now incorporated into the Developmental Therapeutics Program (DTP), Division of Cancer Treatment, has had a comprehensive drug development program that includes the screening of compounds obtained from natural products [7]. Since the inception of the program, approximately 178,802 microbial cultures have been isolated and fermented and 103,272 plants extracted. The fermentation broths and plant extracts have been tested for their cell cytotoxicity and in vivo activity against various animal tumors using standard protocols [10]. During the last 3 years the fermentation broths in many cases have first been tested in various in vitro prescreens (e.g., enzyme inhibition, tubulin binding, phage induction, antimicrobial and antiyeast screens) [6]. Approximately 7 years ago a concentrated effort to evaluate animal products (primarily marine) was initiated and to date 13,751 extracts have been screened and 0.7% showed confirmed in vivo activity.

Many compounds have been isolated from the above-mentioned programs and in addition many natural products are obtained from the NCI worldwide surveillance program which includes agreements with industrial companies, research institutes, universities, and scientists. Some of the more interesting compounds in preclinical drug development that will be discussed are listed in Table 1. Many of the compounds discussed are analogs of earlier compounds which have been prepared in an effort to discover second generation drugs which retain the activity of the parent molecule and have less toxicity.

S. K. Carter et al. (eds.), *New Drugs in Cancer Chemotherapy*

Table 1. Natural products undergoing preclinical drug development at NCI

Compound	NCI No.
Actinomycin pip 1β	107660
Azetomycin 1	244392
Actinomycin S_3	296940
Pepleomycin	276382
Bleomycin BAPP	294979
Tallysomycin A	279496
Aclacinomycin A	208734
7-0-methyl nogarol	269148
Nogamycin	265450
Echinomycin	526417
Valinomycin	122023
Largomycin	237020
Aphidicolin	234714
Neothramycin	285223
Rapamycin	226080
CC-1065	298223
Borrelidin	216128
Eriofertopin	283439
Homoharringtonine	141633
Tripdiolide	163063
Taxol	125973
Baccharin	269757
Isobaccharin	269760
Phyllanthoside	266492
Fagaronine	157995
Psorospermin	266491

Methodology

Natural products, when purified (> 90%), are assigned NSC numbers which are identification codes used by NCI for all compounds studied. NCI prefers materials to be at least 98% pure before assigning NCS numbers; however, because proteins, peptides, polysaccharides, and some other antibiotics do not lend themselves to easy purification or are extremely costly to purify to a state of > 90% purity, they are assigned NSC numbers also. The various protocols for screening these drugs have been established by the Drug Evaluation Branch, NCI [10]. Normally the P388 leukemia assay in mice is the first in vivo test in which a natural product compound is evaluated. However, rational selection can result in using another in vivo tumor as the first screen if there is information on organ distribution, lipophilicity, selective tissue effects, or other antitumor data that indicate that other testing is preferable.

In most cases a material is tested initially against the P388 leukemia (PS) to determine toxicity data even though this may not be the test tumor of greatest interest. If reproducible activity is demonstrated in PS as evidenced by an increase in life span (ILS) of 20% or greater and if the compound has a novel structure, it is tested against a panel of tumors (Table 2). Close analogs of known compounds are tested under special

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